(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 524 150 A1**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: **92810529.5**

(51) Int. Cl.[5]: **A61L 2/18**, A01N 25/30, G02C 13/00, A01N 59/00

(22) Date of filing: **10.07.92**

(30) Priority: **19.07.91 US 733115**

(43) Date of publication of application: **20.01.93 Bulletin 93/03**

(84) Designated Contracting States: **AT BE CH DE DK ES FR GB GR IT LI LU NL PT SE**

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(54) **Improvement in hydrogen peroxide disinfection solutions.**

(57) The efficacy of buffered H_2O_2 disinfecting formulations for contact lenses is improved by incorporating into such formulations a surface active agent.

EP 0 524 150 A1

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The present invention provides an improvement in hydrogen peroxide disinfection solutions. Specifically, the invention provides improvement in such disinfection solutions employed in the disinfection of contact lenses.

Disinfecting solutions for use with contact lenses are well known in the art and the use of such lenses involves a daily disinfecting treatment. Flexible, or soft, contact lenses are generally made from hydrophilic polymers and the hydroxy groups of these lenses attract and retain substantial amounts of water in the plastic which results in difficulties during cleaning and sterilization.

Furthermore, hydrophilic flexible contact lenses have a tendency to complex with and concentrate certain preservatives and disinfecting agents used in sterilizing conventional contact lenses. If these preservatives come into contact with the cornea they can cause severe irritation and burning.

Hydrogen peroxide systems, and particular a 3 % hydrogen peroxide solution, have emerged as the disinfectant of choice for all types of daily and extended wear hydrogen lenses. The primary reason for its increasing popularity is its rapid kill of microbial contaminants and its non-residual character. After hydrogen peroxide disinfects lenses, it can be converted into innocuous by-products which are compatible with ocular physiology. See Krezanoski et al., "Journal of the American Optometric Association", Vol. 59, Number 3, pages 193-197 (1988).

A great deal of patent literature is available concerning hydrogen peroxide contact lens disinfection systems. Reference is made in this respect to the following:
Gaglia, Jr., U. S. Patent No. 3,912,451;
LaRouzie et al., U.S. Patent No. 4,743,447;
Davies et al., International Patent Publication WO 86/05695;
Andermann et al., U.S. Patent No. 4,880,601;
Giefer, U.S. Patent No. 4,585,488.

In general, the hydrogen peroxide systems involve a hydrogen peroxide-containing disinfecting solution into which the contact lenses to be disinfected are placed and allowed to remain for a required period of time. Nascent oxygen is released providing a germicidal effect. Following the requisite time period a purposeful inactivation of the hydrogen peroxide is conducted, for example, with a platinum catalyst. Following inactivation, the contact lens may be reinserted into the eye.

The hydrogen peroxide disinfecting solutions may be of the buffered or unbuffered type. As examples, AO-Sept® is a stabilized 3 % hydrogen peroxide solution made isotonic with sodium chloride and buffered to an approximate pH 6.9 with phosphates. On the other hand, LenSept® is a non-buffered 3 % hydrogen peroxide formulation.

The present invention is based upon the discovery that it is possible to improve the killing effectiveness and the rate of kill of both fungi and bacteria by modifying the buffered hydrogen peroxide disinfecting solution to incorporate therein an ocularly compatible surface active agent in a specified amount. Thus, the invention provides an improvement in a buffered hydrogen peroxide disinfecting solution which comprises incorporating into said solution from about 0.1 % to about 1.0 % by weight of the solution of an ocularly compatible surface active agent. Thus, the invention is directed to, in a buffered hydrogen peroxide formulation for disinfecting contact lenses, the improvement wherein said formulation contains from about 0.1 % to about 1.0 % by weight of the formulation of at least one ocularly compatible surface active agent which improves the killing efficacy of said buffered hydrogen peroxide formulation, and to improved buffered hydrogen peroxide formulations comprising from about 0.1 % to about 1.0 % by weight of the formulation of at least one ocularly compatible surface active agent which improves the killing efficacy of said buffered hydrogen peroxide formulation, and to the use of such formulations for the disinfection of contact lenses.

Gaglia, Jr., U. S. Patent No. 3,912,451 discloses buffered hydrogen peroxide solutions of the type to which the present invention can be applied and for which improvement can be achieved.

By addition of the surface active agent to the buffered hydrogen peroxide disinfecting solution it is possible to improve the killing effectiveness and the rate of kill of both fungi and bacteria.

With most 3 % hydrogen peroxide formulations, there are some viable organisms remaining even after a 30 minute soaking time of the contact lens. However, with the improvement of this invention, it is possible to provide a formulation in which there are no viable organisms after a 30 minute soaking time. With the current peroxide formulations there is a "lag" time between the time when the organisms are placed in the peroxide and the time when actual killing occurs. With the addition of the surface active agent, this "lag" time is reduced significantly and the rate of kill is enhanced.

In the literature it has been indicated that hydrogen peroxide formulations are not effective for contact lenses without a full-strength soaking for a minimum of 55 minutes. With this invention, however, it is possible to reduce considerably the disinfection time and obtain more complete disinfection.

The hydrogen peroxide formulations to which the surface active agent is added are of the buffered type. In general, in formulating such solutions a 3 % by weight hydrogen peroxide solution is formulated to contain

0.85 % by weight soldium chloride. Upon the ultimate conversion of the H_2O_2 to water and oxygen by catalyst this will yield an approximately isotonic saline solution as the final product. With the sodium chloride there is added to the H_2O_2 solution the necessary buffer system to buffer the 0.85 % aqueous sodium chloride solution to the desired pH of about 6.9 to 7.1.

The buffer system may comprise a suitable combination of monobasic sodium phosphate and dibasic sodium phosphate. Other satisfactory buffer systems may be employed which give substantially equivalent results in buffering to a pH of 6.9 to 7. 1. As examples there can be mentioned tartrate, succinate and glycine buffers or the MacIlvaine phosphatecitrate buffer as described in J. Biol. Chem., 183 (1921).

To the solution can also be added a hydrogen peroxide stabilizer such as sodium stannate or sodium nitrate. Such stabilizers are known in the art. In addition, as the stabilizer there can be employed diethylene triamine penta (methylenephosphonic acid) or a physiologically compatible salt thereof (see U.S. Patent No. 4,889,689).

As an example of the buffered type hydrogen peroxide formulation, there can be mentioned the commercially available AOSept® formulation.

In the broadest sense the surface active agents which can be used are those which are ocularly compatible and which function in the buffered hydrogen peroxide formulations to improve the killing effectiveness of such formulations. Preferably the surface active agent is a nonionic surface active agent. As specific examples of the surface active agents the following may be mentioned:

Polyethylene-polyoxypropylene substituted ethylenediamine nonionic surfactants which are more commonly known as "Tetronic®" type surfactants. These are also generally known by the generic name "poloxamine" and are commercially available from BASF-Wyandotte Corp.

Polyoxyethylene-polyoxypropylene nonionic surfactants sold under the trademark "Pluronic®" by BASF-Wyandotte Corp. These surfactants are generally known as "poloxamers " and typically have a molecular weight of between about 2,000 and about 5,000.

Polysorbates, such as "Tween® " surfactants (ICI Americas) including, for example polysorbate 20, 40, 60, 65, 80 and 85.

Tyloxapol, such as "Superinone® " detergent (Winthrop).

Miranol® amphoteric surfactants from Miranol Inc. such as "Miranol®" 2MCA which is lauryl sulfate salt of an amphoteric surfactant derived from coconut imidazoline.

Varonic® LI surfactants such as Varonic® LI-63 and LI-67 which are ethoxylated glyceryl monococoates. These are commercially available from Sherex Chemical Company, Inc..

Varsulf anionic sulfosuccinates such as Varsulf SBFA-30 and Varsulf SBL-203. These are commercially available from Sherex Chemical Company, Inc..

The foregoing are merely illustrative and not exhaustive of the surface active agents which can be employed in the invention.

One skilled in the art will be able to readily determine whether a given surface active agent or mixture of such agents can be employed. First, it is necessary to determine that such agent or mixture of agents is ocularly compatible. Tests for determining such compatibility are well known in the art. Such agent or mixture must not cause irritation or damage to the eye of a contact lens wearer. Secondly, the agent or mixture must be one which improves the killing efficacy of the buffered H_2O_2 formulation. Standard challenge organisms are known against which the buffered H_2O_2 formulation alone and that formulation containing the surface active agent or mixture can be compared. It is not, of course, essential that the agent or mixture of agents improve the efficacy against every challenge organism, it being most important that the overall spectrum of activity be improved.

It is also to be noted that these surface active agents can be employed alone or in combination. Preferred is e.g. a mixture of a poloxamine type and a poloxamer type surface active agent. Also preferred is a mixture of a poloxamine type and a polysorbate type surface active agent.

The surface active agent is added to the hydrogen peroxide formulation in an amount from about 0.1 % to about 1.0 % by weight of the formulation, preferably from about 0.1 % to about 0.6 % by weight of the formulation and more preferred from about 0.1 to about 0.4 % by weight of the formulation.

Particularly suitable for use in the invention are the nonionic poloxamine and poloxamer type surfactants as disclosed in European Patent Application EP-A2-439,429. These materials offer the further advantage of providing conditioning properties for the contact lenses by rendering the contact lens surface more wettable so that proteins, lipids and other tear film substituents do not adhere to and form deposits on the lens surface. Some relevant parts of EP-A2-439,429 are repeated hereinafter:

"The present invention relates to a conditioning solution for contact lenses which comprises an effective amount of a polyoxyethylene-polyoxypropylene substituted ethylenediamine nonionic surfactant having a hydrophile-lipophile balance of seven or below. These surfactants preferably have a molecular weight of between about 3,600 and about 9,000. Such surfactants are typically known generally as "Poloxamine", and sold under the trademark Tetronics® (BASF-Wyandotte Corp.). Preferred are those solutions wherein said polyoxyethy-

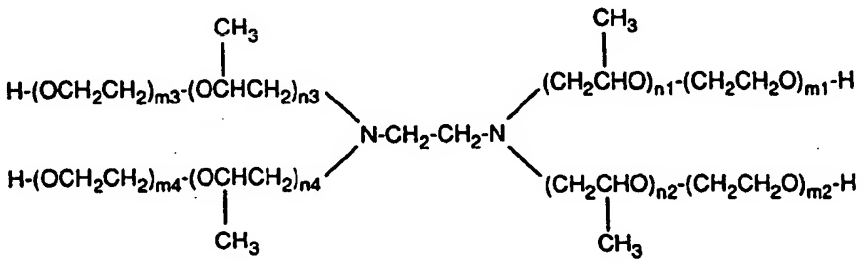
lene-polyoxypropylene substituted ethylenediamine nonionic surfactant has a polyoxyethylene concentration between about 10 % and about 20 % by weight.

The solution may also have an effective amount of a polyoxyethylene-polyoxypropylene nonionic surfactant having a hydrophile-lipophile balance of seven or below and a polyoxyethylene concentration of less than about 20 % by weight. Such surfactants are generally known as "Poloxamers" and sold under the trademark Pluronics® (BASF-Wyandotte Corp.). They typically have a molecular weight of between about 2,000 and about 5,000.

.....

The polyoxyethylene-polyoxypropylene substituted ethylenediamine nonionic surfactant and the polyoxyethylene-polyoxypropylene nonionic surfactant are both surface active agents which have as low a hydrophile-lipophile balance (HLB) as will be tolerated in the formulations. The low HLB values in the surface active agent indicate a high affinity for hydrophobic (lipophilic) surfaces. These surfaces active agents strongly adhere to those hydrophobic regions of the contact lens and render them hydrophilic. This adherence forms a "barrier" to potential absorbance, and keeps them from the surface of the lens. Furthermore, this increase in hydrophilicity simultaneously decreases the thermodynamic having force for protein and lipid absorption, thereby retarding tear film deposits.

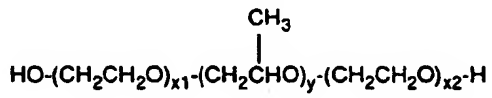
As mentioned hereinbefore the poloxamine type surfactants are more commonly known as Tetronic® type surfactants. The Tetronic® type surfactant is a tetrafunctional block copolymer derived from the sequential addition of propylene oxide and ethylene oxide to ethylenediamine, and is represented by the following structure:



wherein n1 to n4 and m1 to m4 are numbers being a function of the desired molecular weight and the ratio of ethyleneoxy groups to propyleneoxy groups. The preparation thereof can be found in U.S. Patent No. 2,979,528, which is incorporated herein by reference. For convenience purposes, these nonionic surfactants will be identified generally as Tetronic®, with a numeral suffix to identify a particular grade of material as available from BASF-Wyandotte Corp.

It has been surprisingly discovered that only tetronics having a hydrophile-lipophile balance of seven or below are suitable for use in the conditioning solution of the present invention. Such tetronics typically have the molecular weight of between about 3,600 and about 9,000 and include Tetronic 701; 702; 901; 1101; 1102; 1301; 1302; 1501; and 1502 from BASF-Wyandotte.

The poloxamer type surfactants comprise a series of closely related block polymers that may generally be classified as polyoxyethylene-polyoxypropylene condensates terminating in hydroxyl groups. They are formed by the condensation of propylene oxide onto a propylene glyconucleus followed by the condensation of ethylene oxide onto both ends of polyoxypropylene base. The polyoxyethyl hydrophilic groups on the ends of the molecule are controlling length to constitute anywhere from 10 % to 80 % by weight of the final molecule. The structure of the polyethylene-polyoxypropylene nonionic surfactant is preferably as follows:



wherein x1, x2 and y are numbers being a function of the desired molecular weight and the ratio of ethyleneoxy groups to propyleneoxy groups. For convenience purposes, these nonionic surfactants will be referred to herein as Pluronic® generally, with a numerical suffix to identify a particular grade of material as available from BASF-Wyandotte Corp.

It has further been discovered that the polyoxyethylene-polyoxypropylene nonionic surfactant useful in the present invention must have a HLB of seven or below and a polyoxyethylene concentration of less than about

20 % by weight. Such preferred surfactants include Pluronic L61, L81, L101 and L121 from BASF-Wyandotte Corp. These polyoxyethylene-polyoxypropylene nonionic surfactants have a molecular weight of between about 2,000 and about 5,000."

Also particularly suitable for use is a mixture of a poloxamine, e.g. poloxamine 1302 (Tetronic®), and a polysorbate, e.g. polysorbate 80 (Tween® 80), in amounts of about 0.1 % by weight and about 0.4 % by weight respectively.

In order to exemplify the invention, compositions were compared for their relative disinfection capacity in respect to certain challenge microorganisms. The organisms tested are the FDA challenge organisms for disinfection solutions. The time required to kill 50 % of the colony forming units (CFU) in solution was designated as the D-value. The initial solution employed was a commercially available AOSept® solution which is a 3 % buffered hydrogen peroxide solution also containing a hydrogen peroxide stabilizer. The solution of the present invention for comparison is prepared by adding to the commercially available AOSept® initial solution, a mixture of polyoxamine 1302 (Tetronic®) and polysorbate 80 (Tween® 80) in amounts sufficient to constitute 0.1 % and 0.4 % by weight respectively of the formulation. The results are shown in the table below:

	D-VALUE (MINUTES)	
Organism	AOSept®	Composition of the Invention
Pseudomonas aeruginosa	0.54	0.53
Staphylococcus epidermidis	3.4	1.7
Serratia marcescens	2.4	3.5
Candida albicans	10	5.7
Aspergillus fumigatus	12.3	7.1

From the results it can be seen that the modified AOSept® formulation of the invention is particularly effective against fungal spores and staphylococcal strains.

Further tests of the inventors have revealed that the improvement of the invention is applicable to only buffered hydrogen peroxide formulation and not to unbuffered solutions.

For purposes of this test Aspergillus fumigatus was chosen as the test organism. Two representative hydrogen peroxide formulations were used. AOSept®, as previously indicated, is the commercially available 3 % stabilized hydrogen peroxide formulation that is buffered. LenSept® is a commercially available stabilized hydrogen peroxide formulation which is not buffered. These solutions were compared for their killing efficacy as the controls. To each of these control formulations were added specified amounts of various surfactants and the killing efficacy of the resultant solutions was determined. The test results are presented hereinafter. In these tests the D-value is the time necessary to kill 90 % of the active species.

First Control: The D-Value for Lensept® is 8.5 minutes.

The D-Value for Lensept® comprising 0.1 % Tetronic 1302 is 10.8 minutes.
The D-Value for Lensept® comprising 0.4 % Tween 80 is 9.1 minutes.
The D-Value for Lensept® comprising 0.4 % Tyloxapol is 7.9 minutes.
The D-Value for Lensept® comprising 0.4 % Pluronic F 127 is 7.6 minutes.
The D-Value for Lensept® comprising 0.4 % Miranol 2MCA is 8.7 minutes.
The D-Value for Lensept® comprising 0.4 % Varsulf 30 - 40 % is 9.4 minutes.

Second Control: The D-Value for AOSept® is 12.3 minutes.

The D-Value for AOSept® comprising 0.1 % Tetronic 1302 is 6.6 minutes.
The D-Value for AOSept® comprising 0.4 % Tween 80 is 7.7 minutes.

The D-Value for AOSept® comprising 0.4 % Tyloxapol is 8 minutes.
The D-Value for AOSept® comprising 0.4 % Pluronic F 127 is 7 minutes.
The D-Value for AOSept® comprising 0.4 % Miranol 2MCA is 4 minutes.
The D-Value for AOSept® comprising 0.4 % Varsulf 30 - 40 % is 6.9 minutes.

From the above data it can be seen that in the case of the addition of the surfactants to the AOSept® formulation, the killing efficacy was significantly increased in each case compared with the efficacy of the AOSept® alone. However, with the unbuffered LenSept® formulation, the addition of the surfactants either had an adverse affect on the killing efficacy (the time increased) or (in two cases) had a slight affect in improving it.

Claims

1. In a buffered hydrogen peroxide formulation for disinfecting contact lenses, the improvement wherein said formulation contains from about 0.1 % to about 1.0 % by weight of the formulation of at least one ocularly compatible surface active agent which improves the killing efficacy of said buffered hydrogen peroxide formulation.

2. A formulation according to claim 1 wherein the surface active agent is a nonionic surface active agent.

3. A formulation according to claim 2 wherein the surface active agent is a poloxamine.

4. A formulation according to claim 1 wherein a mixture of two surface active agents is employed.

5. A formulation according to claim 4 which employs a mixture of a poloxamine type and a poloxamer type surface active agent.

6. A formulation according to claim 4 which employs a mixture of about 0.1 % by weight of the formulation of a poloxamine and about 0.4 % by weight of the formulation of a polysorbate.

7. A method for improving the efficacy of a buffered hydrogen peroxide formulation for disinfecting contact lenses which comprises incorporating into said formulation from about 0.1 % by weight to about 1.0 % by weight of the formulation of at least one ocularly compatible surface active agent which improves the killing efficacy of said buffered hydrogen peroxide formulation.

8. A buffered hydrogen peroxide formulation comprising from about 0.1 % to about 1.0 % by weight of the formulation of at least one ocularly compatible surface active agent which improves the killing efficacy of said buffered hydrogen peroxide formulation.

9. The use of a formulation according to claim 8 for the disinfection of a contact lens.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92810529.5

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	DE - A - 3 626 082 (HENKEL KGaA) * Abstract; claims * --	1,2	A 61 L 2/18 A 01 N 25/30 G 02 C 13/00 A 01 N 59/00
P,A	EP - A - 0 441 389 (ABBOTT LABORATORIES) * Abstract; claims * --	1,2	
A	US - A - 4 414 127 (FU) * Abstract; claims * ----	1,2	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 L
A 01 N
G 02 C

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	27-10-1992	SCHNASS

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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